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Propargylic Oxidations Catalyzed by Dirhodium Caprolactamate in Water: Efficient Access to α,β-Acetylenic Ketones

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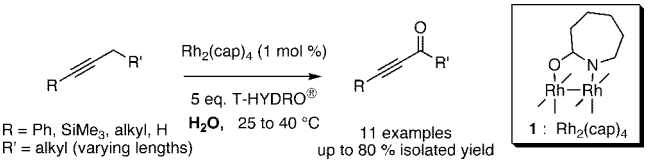

Dirhodium(II) caprolactamate (**1**, $Rh_2(cap)_4$) with 70% w/w aqueous *tert*-butyl hydroperoxide (T-HYDRO) is a highly effective catalytic oxidation protocol for the selective C−H oxidation of alkynes to propargylic ketones. The oxidation occurs readily in aqueous solvent under mild conditions with an inexpensive and easily handled oxidant. α,β-Acetylenic carbonyl compounds are formed in up to 80% isolated yield.

Mild and selective hydrocarbon oxidation methods are an invaluable tool in synthetic organic chemistry. Installing oxygen into a molecule (oxyfunctionalization) is an important form of oxidation for which increasing degrees of selectivity, efficiency, and sustainability are essential.[1] For these reasons, transition-metal-mediated oxyfunctionalization has been a long-standing focus in both academic and industrial research.[2]

Recently, we have reported that dirhodium caprolactamate **1**, $Rh_2(cap)_4$, with *tert*-BuOOH (TBHP) can effectively catalyze allylic,[3] benzylic,[4] and amine oxidations.[5] Initially we thought anhydrous TBHP in decane was necessary to avoid hydrolysis of ligands from the dirhodium catalysts such as **1**. However, we recently found that that $Rh_2(cap)_4$ *is* compatible with 70% aqueous TBHP (T-HYDRO) in allylic oxidations.[6] In efforts to continue improvements in dirhodium oxidation technology, we have found that water can replace organic solvent. Herein, we report the oxidation of alkynes to α,β-acetylenic ketones by T-HYDRO (70% w/w aqueous *t*-BuOOH), catalyzed by **1** with water as the reaction solvent.

Early examples of alkyne oxidations used superstoichiometric amounts of chromium(VI) complexes to afford low yields of ynones.[7] Muzart provided the first example of catalytic propargylic oxidation by using a bis-tributyltin oxide dichromium(VI) complex in conjunction with *t*-BuOOH.[8] Recent propargylic oxidations have made use of *N*-hydroxyphthalimide or *t*-BuOOH with transition metal catalysts [Cr (VI), Cu(II), Fe(II) and Fe(IV)].[9] However, few of these processes show exceptional selectivity, efficiency, and sustainability.

The utility of α,β-acetylenic ketones (ynones) has been reported in the synthesis of biologically relevant molecules such as C-nucleosides,[10] antitumor agents,[11] and insect pheromones.[12] Ynones are also versatile synthons in the preparation of chiral propargylic alcohols,[13] γ-acetylenic enones,[14] Diels−Alder adducts,[15] and a variety of heterocyclic compounds.[16] Traditionally, they are prepared in two steps by terminal acetylide anion addition to aldehydes, followed by oxidation of the resultant alcohol.[17] Ynones can also be prepared in a single step by stoichiometric acylation of organometallic alkyne equivalents[18] or catalytic metal-mediated coupling,[19] although many of these one-step methods are limited to only aryl-substituted substrates.

We have found that oxidation of 4-octyne (**2**) with 1.0 mol % of **1** and T-HYDRO in a chlorinated hydrocarbon solvent (1,2-dichloroethane, DCE) at 40 °C afforded ynone **3** in 86% yield. However, the same oxidation in *water* furnished **3** more rapidly and in higher yield (89%, Scheme 1).[20] Moreover, water acted as a heat sink for the exothermicity of dirhodium(II)-

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(13) For recent examples, see: (a) Baker, J. R.; Thominet, O.; Britton, H.; Caddick, S. *Org. Lett.* **2007**, *9*, 45. (b) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2006**, *128*, 12660.
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(17) For recent examples, see: (a) Waddell, M. K.; Bekele, T.; Lipton, M. A. *J. Org. Chem.* **2006**, *71*, 8372. (b) Wang, C.; Forsyth, C. J. *Org. Lett.* **2006**, *8*, 2997. (c) Zhang, X. X.; Sarkar, S.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 236.
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(19) For examples, see: (a) Alonso, D. A.; Nájera, C.; Pacheco, M. C. *J. Org. Chem.* **2004**, *69*, 1615. (b) Chowdhury, C.; Kundu, N. G. *Tetrahedron* **1999**, *55*, 7011.
(20) Product formation was monitored by gas chromatography.

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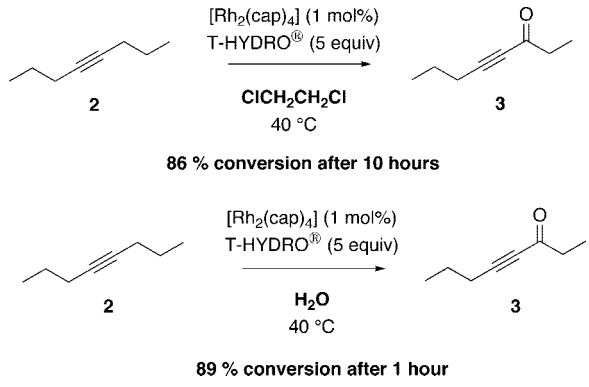
SCHEME 1



mediated decomposition of TBHP, allowing oxidation on a larger scale than was allowable in organic solvents.[21]

Upon closer inspection of the oxidation in water, we observed that the reaction medium was biphasic in that the organic substrate was insoluble in the water layer. Additionally, the oxidized form of $Rh_2(cap)_4$ (Rh_2^{5+}), identified by its a characteristic deep red color, was almost completely dissolved in the water. Analysis of the aqueous layer by UV−visible spectroscopy revealed the characteristic signature of Rh_2^{5+} with λ_{max} at 505 and 971 nm.[22]

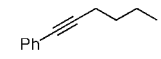
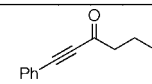
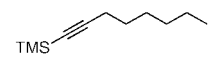
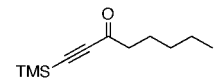
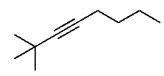
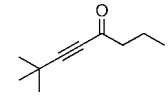
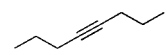
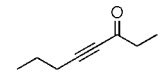
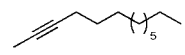
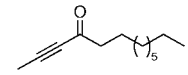
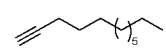
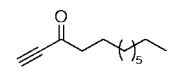
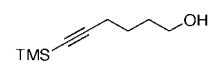
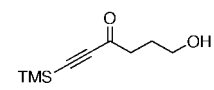
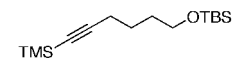
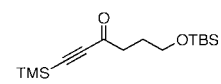
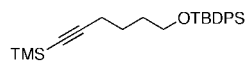
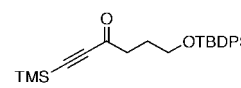
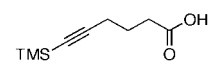
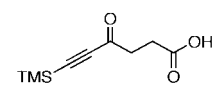
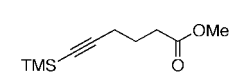
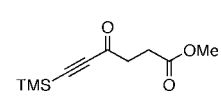
Reaction optimization was attempted by performing a screening of inorganic salts based previous reports of the use of additives in allylic and benzylic oxidations.[4] Several salts were detrimental to the reaction (Na_2CO_3, $NaHSO_4$, Cs_2CO_3, and K_2CO_3), and all others gave yields comparable to the that of the oxidation without additive (NaCl, $NaHCO_3$, H_2KPO_4, $HK_2PO_4 \cdot H_2O$).[23] Overall, we found no significant improvement to the original oxidation of **2** using base additives in water or in organic solvent.

Given the effectiveness of the oxidation of **2** in water (Scheme 1), we employed the same conditions in a survey of other propargylic substrates (Table 1). Entries 1−6 summarize the results obtained with varying substitution on the acetylenic terminus. When the alkyne is substituted with phenyl, *tert*-butyl, trimethylsilyl, and *n*-propyl groups, the oxidation affords good isolated yields of the resulting ynones (entries 1−4). In the oxidation of 2-tridecyne (entry 5), the internal methylene is selectively oxidized over the competing methyl group. Oxidation of the terminal alkyne in entry 6 afforded the corresponding ynone in only moderate yield, yet it was comparable to the yield of this product in previously reported oxidations.[8b,c,9d–f]

The remaining entries in Table 1 showcase a sampling of functionality tolerated under aqueous oxidation conditions. We found that a pendant primary alcohol (entry 7) was compliant to our conditions in only modest yield. When the same alcohol was protected as a *tert*-butyldimethylsilyl (TBS) ether, the protecting group was cleaved as a result of the slightly acidic (pH 4−5) reaction medium, and a small amount of alcohol oxidation products was observed.[24] Using a more acid-tolerant protecting group to mask the alcohol (entry 8), the desired ynone was cleanly furnished in much higher yield. Finally, the $Rh_2(cap)_4$-catalyzed propargylic oxidation conditions were amenable to both the pendant carboxylic acid in entry 10 and the methyl ester in entry 11 (Table 1),[25] whereas a previously reported propargylic oxidation by TBHP was ineffective in the presence of carboxylic acid functionality.[9e]

The biphasic nature of these oxidations allowed us to reuse or "recycle" the catalyst by extraction of the Rh^{5+}-containing aqueous layer from one reaction for use in the next (Scheme 2). In this series of oxidations, **4** was treated under standard conditions (1.0 mol % of **1**, 5.0 equiv T-HYDRO, in water) to afford **5** in 70% yield. Following extraction of **5** with ether, the aqueous layer from the first reaction was drained into a vessel containing **6** and an additional 5.0 equiv of the oxidant was added to initiate the second oxidation. The product, **7**, was

TABLE 1. Propargylic Oxidation Catalyzed by $Rh_2(cap)_4$ (1)[a]

entry	reactant	time (h)	product	yield[b] (%)
1		2		80
2		2		77
3		2		73
4		1		79 (89)[c]
5		12		62
6		60		43
7		5		42
8[d]		12		39
9		20		66
10		15		62
11		30		79

[a] Reactions were performed by addition of T-HYDRO (5.0 equiv) to a vigorously stirred mixture of **1** (1.0 mol %) and the alkyne (1.0 equiv, 0.54 M) in water followed by heating to 40 °C. [b] Isolated yields after column chromatography. [c] GC yield, as determined by internal standard. [d] This oxidation was stirred at ambient temperature (25 °C).

(21) Under the same aqueous conditions, we were able to scale the oxidation by a factor of 8 (1 mmol of 4-octyne gave 79% isolated yield and 8 mmol of 4-octyne gave 75% isolated yield of 4-octyn-3-one).

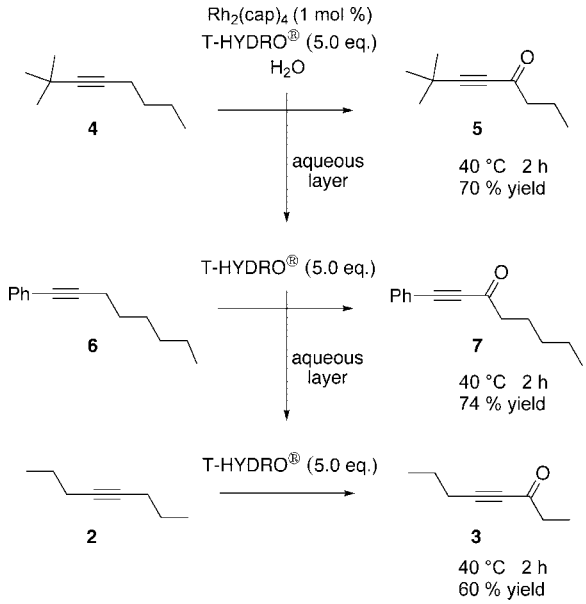
(22) Catino, A. J.; Nichols, J. M.; Forslund, R. E.; Doyle, M. P. *Org. Lett.* **2005**, *7*, 2787.

(23) The experiment was performed with 4-octyne (**2**), 0.54 M in water, with 1 mol % $Rh_2(cap)_4$ (**1**) and 5 equiv of T-HYDRO. To each separate reaction was added 1 equiv of the respective salt, and the mixture was then heated to 40°C for 1 h.

(24) The aldehyde and carboxylic acid were observed by ^1H NMR.

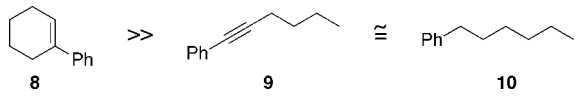
(25) The oxidation of an electron-deficient alkyne, 2-octynoic acid methyl ester, was sluggish, proceeding in only 50% conversion and furnishing 30% isolated yield of 3-oxo-2-octynoic acid methyl ester.

SCHEME 2



isolated in similar reaction time and in comparable yield. Subsequently, we found that the resultant aqueous layer from the formation of **7** was able to catalyze yet another oxidation. However, in the oxidation of **2** a color change could be observed in the aqueous layer, and the yield of **3** was diminished, indicating the loss of the active dirhodium species, but only after 1.0 mol % of **1** successfully catalyzed three different C−H oxidations.

The aqueous propargylic oxidation was directly compared to allylic[3] and benzylic[4] oxidations catalyzed by **1**. From the analysis of the initial rates of consumption of **9** and **10**, the reactivity of the propargylic substrate **9** was found to be comparable to that for the benzylic substrate **10** under aqueous oxidation conditions. In the comparison of **8** and **9**, the consumption of allylic substrate **8** proved to be considerably faster than the consumption of **9** (Figure 1).

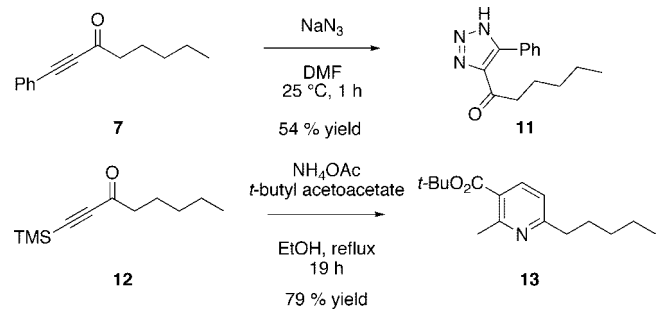


[a] Based on the relative consumption of starting material
[b] In the oxidation with **1** and T-HYDRO® in water at 25 °C

FIGURE 1. Relative initial reactivity[a] of C−H oxidation in allylic, benzylic, and propargylic oxidation.[b]

With an assortment of α,β-acetylenic ketones in hand, we demonstrated the utility of these compounds in the preparation of two polysubstituted heterocycles (Scheme 3). In the first example, ynone **7** was treated with sodium azide in DMF to effect a rapid [3 + 2] cycloaddition to form the 4,5-disubstituted acyl triazole **11** in moderate yield. We were also able to prepare a 2,6-disubstituted nicotinic acid derivative **13** in one step using a procedure adapted from Bagley and co-workers.[16b] This one-

SCHEME 3



pot, three-component transformation using ynone **12**, ammonium acetate, and *tert*-butyl acetoacetate was accomplished with complete regiocontrol and in good yield.

In summary, we have developed an efficient oxidation of alkynes to ynones employing a mild, inexpensive oxidant in water. As a solvent, water not only is beneficial in terms of sustainability but also has a positive effect on the reaction rate in this oxidation. Additionally, using this method, the catalyst, $Rh_2(cap)_4$ (**1**), is readily recycled for use in additional oxidations.

Experimental Section

General Procedure for Propargylic Oxidations Catalyzed by Dirhodium(II) Caprolactamate in Water. The alkyne was stirred vigorously in water (0.54 M with respect to the alkyne) at room temperature in a screwcap vial. $Rh_2(cap)_4$ (1.0 mol %) was added to the vial followed by dropwise (2 drops/s) addition of 5.0 equiv of T-HYDRO. The reaction was slightly exothermic, and the mixture bubbled and became dark purple-red in color. The vial was loosely capped and stirred at room temperature or heated to 40 °C while being monitored by TLC and gas chromatography. Upon consumption of the starting alkyne, the reaction was extracted twice into diethyl ether. The organic extracts were combined, dried over anhydrous $MgSO_4$, filtered, and then concentrated under reduced pressure to a crude oil, which was purified via silica gel chromatography (hexanes/ethyl acetate) to afford the desired product.

Sample Characterization for 1-Phenyl-1-octyn-3-one (7). R_f 0.55 (10% ethyl acetate/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (comp, 2 H), 7.43 (comp, 1 H), 7.37 (comp, 2 H), 2.66 (dd, J = 7.6 7.6 Hz, 2 H), 1.75 (dq, J = 7.6 Hz, 2 H), 1.37−1.33 (comp, 4 H), 0.92 (dd, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.3, 133.0, 130.6, 128.6, 120.0, 90.5, 87.8, 45.5, 31.1, 23.8, 22.4, 13.9; FTIR (thin film) 2960, 2928, 2199, 1669, 1488, 1280, 1132, 1072 cm^{-1}. Exact mass calculated for $C_{14}H_{16}O$ (EI) 200.1201, found 200.1201.

Supporting Information Available: Procedures and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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